October 29, 2004

Mr. Paul Tilton
Chief, OB/GYN, Gastroenterology and Urology Devices Branch (HFZ-332)
Division of Enforcement A
Office of Compliance
Center for Devices and Radiological Health
Food and Drug Administration
2098 Gaither Road
Rockville, MD 20850

Re: *Response to Warning Letter Received October 11, 2004*

Dear Mr. Tilton:

On October 11, 2004, Lifecore Biomedical, Inc. received a Warning Letter dated October 8, 2004, that cited alleged deficiencies in Lifecore's reporting of certain complaints of serious injuries and malfunctions in association with Lifecore's GYNECARE INTERGEL® Adhesion Prevention Solution ("INTERGEL"). This letter and attachment constitutes Lifecore's response to the Warning Letter.

I. Summary of Response

Respectfully, Lifecore disagrees with the assertions in FDA's letter that the specified complaints should have been reported as MDRs under 21 C.F.R. Part 803. For each of the complaints cited in the Warning Letter, Lifecore complied with its reporting obligations under FDA's MDR regulations, 21 C.F.R. §§ 803.50 and 803.20(c).

In sum, with regard to FDA's allegations that two complaints should have been reported as "malfunction" MDRs, FDA has failed to follow the definition of "malfunction" in 21 C.F.R. § 803.3(n). The definition of "malfunction" is based on the device's performance for its labeled intended use. But FDA has cited two complaints involving uses of the device outside the intended use of INTERGEL in open, conservative gynecological surgery. Thus, FDA's allegations that these complaints are reportable malfunctions are contrary to the regulation. With regard to the complaints that FDA claims should have been submitted as a "serious injury" MDR, Lifecore notes that every one of those complaints had been submitted to FDA in reports to the PMA file prior to the May 2004 inspection. In addition, for several of these complaints, Lifecore solicited, received, and relied on guidance provided by CDRH officials on whether or how to submit these complaints to FDA in accordance with FDA's regulations. In light of these facts, Lifecore believes that FDA's issuance of this Warning Letter is unwarranted and unfair.

Nevertheless, in an effort to resolve this matter, Lifecore will implement several corrective actions, including substantial revisions to the company's policies regarding the reporting of complaints received about INTERGEL. The changes to the reporting SOPs will address the issues of reportability cited in FDA's letter. The corrective actions are further described below.

Lifecore requests that FDA post this letter response on its website without the accompanying attachment.

II. Background Relating to Complaint Reporting Interactions with FDA

Since receiving premarket approval for INTERGEL, Lifecore has been diligent and proactive in reporting to FDA complaints alleging serious injury or malfunction, submitting them in periodic reports to the PMA file and in MDR reports in accordance with FDA's regulations. Over 86,000 units of INTERGEL have been sold worldwide since 1998, and Lifecore has received approximately 375 reports of product complaints. Of these complaints, 128 were filed as MDRs (over 34%), and the remainder of the complaints were reported to the agency in periodic submissions to the PMA file. This record reflects Lifecore's diligence and good faith in seeking to comply with the MDR reporting obligations.

The difficulty of making these reportability decisions is evident in the fact that the Office of Compliance Warning Letter disagrees with the FDA investigator on 3 of 9 complaints listed in the Notice of Inspectional Observations ("483") issued to Lifecore on May 17, 2004, that the Warning Letter rejects previous guidance provided to Lifecore by both the Office of Device Evaluation ("ODE") and the MDR staff, and that the Warning Letter essentially overrules the medical judgment of two physicians who reviewed these complaints in accordance with 21 C.F.R. § 803.20(c)(2). Given this difficulty, on several occasions, Lifecore sought input from FDA regarding the proper approach to reporting specific complaints. Whenever such guidance was obtained from FDA, Lifecore complied with the guidance provided.

The thirteen complaints cited by FDA in the October 8 letter are no exception. To be clear, every complaint listed in FDA's letter was submitted to FDA and thus known to the agency prior to the inspection conducted in May 2004. Each of these complaints was communicated to FDA in a periodic report, supplemental application, or other report filed with the agency -- often on multiple occasions. In several cases, these submissions triggered ODE requests for additional information, and Lifecore engaged in substantive discussions with ODE personnel about the information contained in these complaint files. On some occasions, Lifecore obtained direction or guidance from CDRH as to the appropriate way to report the events.

Specifically, FDA's Warning Letter cites four complaints that were received by Lifecore prior to the final approval of INTERGEL for commercial distribution and marketing in the United States (H01-000063, H01-000064, H01-000065, H02-000001). INTERGEL

received premarket approval from FDA on November 16, 2001. However, the approval letter specifically stated that "before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form." Until Lifecore fulfilled this PMA amendment requirement, the product was not authorized for commercial distribution or marketing in the United States. On January 11, 2002, Lifecore submitted the PMA amendment with final labeling to FDA and began marketing the product in the United States. In the interim, however, the company received reports of product complaints from experience outside of the United States. Because the MDR regulation states that manufacturers are required to submit MDRs related to "a device *marketed* by the manufacturer," Lifecore believed that the MDR regulation did not apply. 21 C.F.R. § 803.50(a) (emphasis added). On November 28 and 29, 2001, Lifecore consulted with a senior CDRH/ODE official regarding the proper approach to submitting the ex-US complaints that were received in the interim between the November 2001 approval letter and the filing of the PMA amendment with final labeling that would allow the launch of US marketing. Lifecore was instructed by CDRH to report these types of pre-launch complaints in a PMA "progress report." Lifecore complied by initially submitting a progress report on December 18, 2001, and then a periodic report on February 28, 2002 entitled "Complaints Prior to U.S. Commercialization (May 5, 1998 through January 11, 2002)." The latter report listed each of the four complaints now at issue. Following that report, Lifecore then engaged in multiple discussions with FDA about these events, submitted additional documentation in response to ODE requests, and included the four events in no fewer than six additional submissions to FDA. FDA has thus been aware of these events for years and advised Lifecore on the approach Lifecore should follow to submit such pre-launch complaints. At no point during this long history did FDA ever direct Lifecore to submit these complaints as MDRs. Nevertheless, FDA has now issued a Warning Letter to Lifecore that cites these very complaints. Moreover, these four complaints were not cited on the 483, and thus Lifecore had no opportunity to respond to FDA concerns about their potential reportability prior to their appearance in the Warning Letter. In light of this history, Lifecore believes it was unwarranted to cite these complaints in the October 8 letter.

Similarly, Lifecore contacted CDRH on March 6, 2003 in regard to complaint H03-000042. After describing the event to a member of CDRH's Office of Surveillance and Biometrics ("OSB"), Lifecore was told that the event could properly be considered not reportable. Nevertheless, 18 months later, in the September 2004 teleconference between Lifecore and FDA, FDA's Office of Compliance said that Lifecore cannot rely on informal guidance provided by FDA's MDR staff, and that such informal guidance does not preclude the agency from finding a complaint to be reportable as an MDR. Although we recognize that the agency is not necessarily bound by informal guidance provided by agency employees, it is unfair and an abuse of discretion to issue a Warning Letter on a matter where a company has sought FDA's input and acted in specific reliance on the agency official's guidance.

On another occasion, on September 25, 2002, a meeting with Lifecore and FDA was convened to discuss the post-marketing complaint experience with INTERGEL. The company again requested guidance from CDRH staff on the proper application of the MDR regulations for complaints received for INTERGEL. An OSB official advised Lifecore as follows:

- A "serious injury" is defined as an event requiring an intervention, such as a second surgery.

- Lifecore should rely on the judgment of qualified medical professionals to determine the cause of a reported complaint, and to determine whether or not it is reasonable to conclude that the product may have contributed to the reported event.

- Complaints of post-operative pain do not alone constitute serious injury and should not therefore be reported as MDRs.

Lifecore has relied on this guidance when assessing the reportability of complaints. FDA's Warning Letter, however, disregards the guidance FDA provided to Lifecore and changes the criteria for Lifecore's reporting. Most notably, FDA's Warning Letter reaches a determination that various events should have been reported by essentially overruling the documented judgments of qualified medical professionals who reviewed the complaints and determined that the events in question did not involve serious injury or that INTERGEL did not cause or contribute to the event.

In response to the 483 issued to Lifecore in May 2004, Lifecore requested an in-person meeting to discuss the inconsistent and conflicting FDA expectations for MDR reporting by Lifecore in order to obtain a clear understanding of FDA's expectations for handling INTERGEL complaints. FDA refused to provide such an opportunity. Instead, the agency provided Lifecore only with the opportunity to have a teleconference with agency officials, which occurred on September 2, 2004. Even then, FDA informed Lifecore that the agency would not provide Lifecore with any guidance on MDR reporting and would not discuss the complaints cited in the 483 one by one. During the teleconference, the agency provided no specific guidance to Lifecore on these reporting issues. Further, although an FDA official committed to Lifecore that the agency would "keep the lines of communication open" in response to Lifecore's request for an in-person meeting after FDA had reviewed the company's response to the 483, FDA did not honor that commitment. Instead, FDA issued a Warning Letter on October 8.

The agency's letter includes six complaints that were not included in the 483 and not raised during the teleconference. In addition, the Warning Letter reclassified one complaint on the 483 from an alleged serious injury MDR to a malfunction MDR. Therefore, with respect to these complaints, FDA did not provide Lifecore with any prior opportunity to respond to FDA's allegations before the agency issued a Warning Letter. Under these circumstances, for FDA to issue a Warning Letter is not only surprising and

disappointing, but also unfair and inconsistent with the promise of open lines of communication.

III. Discussion of Complaints Cited in the Warning Letter

Lifecore believes that FDA is incorrect in applying the MDR reporting criteria to the facts of these thirteen complaints. For the reasons summarized below and discussed in detail in the Appendix, for each complaint in question, Lifecore has complied with its obligations to report complaints in accordance with all applicable regulations.

First, with respect to the complaints that FDA claims should have been submitted as serious injury MDRs, Lifecore agrees with FDA that four of these events met the criteria for a "serious injury" under the MDR reporting regulations. However, as discussed above, these events occurred and were received by Lifecore prior to commercial marketing of the device in the United States, and Lifecore was instructed by ODE to submit such pre-launch events in a progress or periodic report to the PMA rather than as MDRs. By using this route, ODE personnel (to whom the INTERGEL application had just been transferred from another reviewing division) were able to review and evaluate the events in an expeditious and efficient manner. For all other complaints cited in the Warning Letter, Lifecore consulted with qualified medical professionals with respect to the determination as to the reportability of the complaint pursuant to 21 C.F.R. § 803.20(c)(2). For each event, a medical professional reached a reasonable conclusion that the complaint did not involve serious injury as defined by 21 C.F.R. § 803.3(bb), or that INTERGEL did not cause or contribute to the complaint as defined by 21 C.F.R. § 803.3(d). Accordingly, Lifecore reached a reasonable conclusion that each of these events was not required to be submitted as an MDR pursuant to 21 C.F.R. § 803.20(c)(2). Notwithstanding that, and even though an OSB official had advised Lifecore (as discussed above) to follow the medical opinion procedure in making reportability determinations for INTERGEL, FDA has now essentially overruled the reasonable medical conclusions of the consulting physicians with little or no explanation about the reasons for such rejection.

Second, Lifecore disagrees with FDA's conclusion that INTERGEL malfunctioned in the two complaints identified in the Warning Letter. FDA's regulations define a reportable malfunction as "the failure of a device to meet its performance specifications," which include all claims made in the labeling of the device, or "otherwise perform as intended." 21 C.F.R. § 803.3(n). FDA's regulation clearly states that the "intended performance of a device refers to the intended use for which the device is labeled or marketed." 21 C.F.R. § 803.3(n).

In both complaints cited in the Warning Letter, the product was used in surgical procedures that were outside "the intended use for which the device is labeled." INTERGEL is labeled for use only in "open, conservative gynecological surgery," but these two complaints involved hysterectomy (a non-conservative procedure) and laparoscopic appendectomy (which is neither "open" nor "gynecological surgery"). FDA

is therefore acting contrary to its own regulation in alleging that these complaints involved a device "malfunction" required to be reported under Part 803.

With regard to complaint H02-000095, FDA appears to take the position that the presence of INTERGEL in the peritoneal cavity following surgery is a malfunction. However, the labeling of INTERGEL clearly indicates that the solution is meant to remain in body to prevent the formation of post-surgical adhesions. The labeling states that data from animal studies suggest "90% [of INTERGEL] clearing from the peritoneal cavity in approximately 6 to 8 days" in humans. The labeling thus indicates that INTERGEL is expected to remain in the body after surgery, with at least 10 percent expected to remain more than 8 days after surgery. Accordingly, even assuming the substance reported in this complaint was INTERGEL, the product's presence would not have been a "malfunction." Moreover, the physicians used INTERGEL after performing a laparoscopic appendectomy whereas INTERGEL is indicated for "open ... gynecological surgery." Therefore, the product should not be deemed to have "malfunctioned" when it was used for a procedure outside of "the intended use for which the device is labeled or marketed." 21 C.F.R. § 803.3(n).

With regard to Complaint No. H02-000074, it is in the October 8 letter that FDA for the first time identifies this report as an alleged malfunction. This complaint involved the use of INTERGEL following a hysterectomy, which is non-conservative surgery. The INTERGEL labeling, however, states that it "is indicated for use in patients undergoing *open, conservative gynecologic surgery* as an adjunct to good surgical technique to reduce post-surgical adhesions" (emphasis added). The labeling also provides a clear warning that "The safety and effectiveness of GYNECARE INTERGEL Solution has not been studied in patients undergoing hysterectomy procedures ..." Therefore, because use of INTERGEL following this hysterectomy procedure was not consistent with "the intended use for which [INTERGEL] is labeled or marketed," this was not a reportable "malfunction" as defined by FDA's regulations. 21 C.F.R. § 803.3(n). In addition, the fact that adhesions were more severe after the hysterectomy does not mean that INTERGEL malfunctioned. The labeling does not claim that INTERGEL will prevent post-surgical adhesions, or prevent more severe adhesions, but only that it is indicated "as an adjunct to good surgical technique to reduce post-surgical adhesions." Further, the qualified medical professional reviewing this case concluded that INTERGEL did not cause the adhesions or make them worse, but instead attributed the complaint to the surgical procedure itself. Accordingly, these facts support Lifecore's conclusion that the product did not malfunction.

Moreover, even assuming these cases could be considered a "malfunction," neither of these cases would be likely to cause or contribute to death or serious injury if the situation were to recur. Therefore, neither of these complaints constitutes a reportable malfunction pursuant to 21 C.F.R. §§ 803.20(b)(3)(ii), 803.3(n).

Attached as an Appendix is a discussion of each complaint cited in the Warning Letter with a full explanation of the facts which confirm that Lifecore complied with its reporting obligations in each case.

IV. Corrective Actions

Lifecore has considered FDA's letter and believes that the complaints cited were not required to be submitted as MDRs. Nevertheless, in an effort to resolve this matter to the satisfaction of FDA and assure compliance with MDR reporting requirements as FDA is now applying them to INTERGEL, Lifecore intends to take the following corrective actions.

First, Lifecore will submit the thirteen cited complaints as MDR reports.

Second, Lifecore will amend its general SOP for MDR reporting to clarify that the SOP will apply to all complaints received after the date of product approval, including complaints received prior to the launch of commercial marketing in the United States but after the approval date.

Third, Lifecore will implement a new SOP specifically for INTERGEL complaints. Lifecore will submit this SOP to FDA by November 12, 2004. The new SOP will include several provisions that are directly responsive to FDA's concerns, including the following: (1) Lifecore will no longer rely on the analysis of a qualified medical professional to determine the reportability of complaints pursuant to 21 C.F.R. § 803.20(c)(2). Instead, the company will report all complaints of serious injury associated with the INTERGEL device, regardless of whether or not a qualified medical professional could reach a reasonable conclusion that INTERGEL did not cause or contribute to the event. (2) Lifecore will report as a malfunction MDR all complaints that allege an increased number or severity of adhesions following use of INTERGEL, and all complaints that allege the continued presence of INTERGEL in the body during a subsequent surgical procedure following the use of INTERGEL in the initial procedure, even if the complaint involves use of the product outside its labeled indication for use.

Fourth, the company will engage an outside consultant (1) to assist in revising the general SOP for MDR reporting and implementing the SOP specific to INTERGEL reporting, and (2) to retrain Lifecore's MDR staff on the standards for MDR reporting and on the revised SOPs.

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Lifecore continues to be committed to assuring that FDA has accurate and timely information about the safety and efficacy of the company's products. By taking these corrective action steps, Lifecore seeks to assure that product complaints involving INTERGEL are reported in accordance with the MDR reporting regulations and the additional principles articulated in FDA's letter.

If FDA has any questions about this response or the corrective actions, Lifecore requests an opportunity for an in-person meeting with agency officials in order to facilitate a prompt resolution of these issues and clear understanding for ongoing reporting.

Lifecore requests that this response letter without the accompanying Appendix be posted on FDA's website along with the Warning Letter.

Sincerely,

Dennis J. Allingham
President and CEO
Lifecore Biomedical, Inc.

cc: Ellen J. Flannery, Esq., Covington & Burling